



FOOD AND DRUG ADMINISTRATION

CENTER FOR BIOLOGICS EVALUATION AND RESEARCH

MEMORANDUM

Date: February 2, 1998

To: Fred Miller, BLA Committee Chairman, HFM-561

From: Janice Brown, BLA Committee Member, HFM-206 *JB*

Through: Julia Lukas Gorman, Chief, Branch 1, HFM-206 *JLG*

Subject: Review of Biologics License Application (BLA) from Novartis Pharmaceuticals Corporation for the manufacture, formulation, fill, lyophilization, and packaging of Simulect™; Reference Number 97-1251

My review includes of an evaluation of the following sections submitted in the Chemistry, Manufacturing, and Control section of the BLA: Volume 2, Sections 2.2 to 2.8, Volume 3, Sections 3.1-3.7, Volume 4, Sections 4 and 5, Volume 8, Appendix E, Volume 14, Appendix G.

I have separated my review into two sections, the first section are questions related to the submission that can be addressed in an information request letter and/or during their pre-license inspection and the second section is a narrative of my review. After review of the submission, I have the following questions and comments.

I. Outstanding Issues that can be addressed in the pre-license inspection and/or Information Request letter.

1. Please review the process validation for the _____ column. The firm should have supporting data demonstrating the performance of the column over the proposed lifetime of the column. The performance should include the following: (1) an evaluation of the contaminate removal from the harvest; (2) cleaning validation and sanitization effectiveness using _____ (3) bacteriostatic performance of _____. The actual process parameters (protein load capacity, flow rates, elution profiles) should be used in these evaluations.

2. Please review the process validation for the _____ column. The firm should have supporting data demonstrating the performance of the column over the proposed lifetime of the column. The performance should include the following: (1) an evaluation of the removal of _____, and _____

_____ (3-37) from the product; (2) cleaning validation of the column resin; and (3) sanitization effectiveness and bacteriostatic performance of _____. The actual process parameters (protein load capacity, flow rates, elution profiles) should be used in these evaluations.

3. Please review the process validation for the _____ column. The firm should have supporting data demonstrating the performance of the column over the proposed lifetime of the column. The performance should include the following: (1) an evaluation of the removal of _____ (3-37) and _____ (3-36); (2) cleaning validation of _____; (3) sanitization effectiveness of _____ and (4) bacteriostatic performance of _____. The actual process parameters (protein load capacity, flow rates, elution profiles) should be used in these evaluations.

4. Please review the process validation for the _____ column. The firm should have supporting data demonstrating the performance of the column over the proposed lifetime of the column. The performance should include the following: (1) an evaluation of the removal of _____ (2) cleaning validation of the column resin; (3) sanitization effectiveness of _____ and (4) bacteriostatic performance of _____. The actual process parameters (protein load capacity, flow rates, elution profiles) should be used in these evaluations.

5. Volume 4, page 3-690 includes a schematic of the _____ filling line in Room _____ illustrating different air cleanliness zones. Following filling, partially stoppered vials are transferred from Zone - (U.S. _____) to the lyophilizers which are located in Zone - (U.S. _____) under laminar flow. Where product is directly exposed the environment, we recommend that these areas be classified as Class 100. Although the European Community allows for dynamic and static environmental monitoring, we recommend that classified areas be monitored for viables and nonviable particulates during operations.

6. Volume 2, page 3-129 describes the air quality classification of various rooms in the _____ facilities. The area classifications are listed as critical, controlled, or unclassified. The monitoring frequency is monthly for controlled areas and twice a month for critical areas. The firm should be advised that CBER recommends in critical areas viable and nonviable monitoring should be performed daily during dynamic conditions.

7. The submission did not describe viable limits, pressure differentials, or air flow rates in critical and controlled areas. During the prelicense inspection, please review the HVAC

(re)validation and the most current 6-12 months of environmental monitoring for the following areas:

a. Class — critical area (Room —) for the — filling line.

b. the laminar flow area in Building — in Room — where compounding is performed.

c. Building — (— site), suites — and —

8. Volume 4, page 3-671 includes an European Union (EU) air cleanliness table. The table indicates that a Grade D area has a — micron nonviable specification of — during static conditions. The firm should be advised that the European Community (EC) Guide does not define an operational specification for a Grade D area, therefore, this area does not meet the U.S. Class 100,000 standard for nonviable particulates. Additionally, the EC viable limit for a Grade D area is 200 cfu/m³ (5.7/ft³). The U.S. standard for viable limits is 2.5 cfu/ft³ (88.3 cfu/m³).

9. Volume 4, page 3-678 describe the media fill process. Initial qualification of filling line — was performed in February 1992 with — and — vials. Subsequent to the initial qualification, media fills are perform — Please review the media fill procedure and compare the process to the Simulect fill and the raw data for media fills for the most current 12 months (see V4, page 3-678).

10. Volume 4, pages 3-673 and 3-674 describe the results of a validation study supporting the following hold periods: the — hold from compounding to the first 0.2 micron filtration, the — hold between the beginning and end of the second sterile filtration, and the — lyophilization hold after vial filling prior to lyophilization. — test microorganisms /

— were inoculated into a — bulk drug product solution for — at — . The submission states that no significant increase was noted. Although they evaluated that the bulk solution did not promote growth of microorganisms, some product evaluation should be performed. During the pre-license inspection, please review validation data supporting that the product characteristics were not affected during these holds.

11. Volume 4, page 3-674 include in-process bioburden specifications during the hold periods. Samples are taken on the upstream side of the first and second 0.2 micron filter. The specifications are total aerobic count is — and gram negative rods is — for the first prefiltration sample and a total aerobic count is —

_____ for the second prefiltration sample. Please review the historical manufacturing data to verify these specifications.

12. Volume 2, pages 3-339 to 3-346 describe in-process holds during the manufacturing process. Please review data supporting the following in-process product hold periods: _____ at _____ for the _____ column pool (Step 1); _____ at _____, following the filtration operation in Step 2; _____ at _____ following filtration in Step 3; _____ at _____ at steps 5, 6, 8, and 8.

13. Volume 2, pages 3-139 to 3-141 describe buffer hold periods. Please review the data support the following buffer hold periods: _____ at _____ C for _____ and _____ at _____ for _____ and _____ and 30 days at _____ C, _____ at _____ C, and _____ at _____ for _____. No time or temperature specifications were provided for _____, _____, _____, _____ and _____. Volume 2, page 3-393 includes bioburden testing for production batches _____ and _____. The submission describes corrective action for sanitization procedures for tanks used in manufacturing. In addition to a validated sanitization procedure, please review hold period for WFI.

14. There are several filtration steps during the manufacture of basiliximab. Although the filters are 0.22 micron, there is an associated bioburden level in the drug substance. The drug substance endotoxin and bioburden specification is aerobic organisms - _____ anaerobic organisms - _____ and _____ None detectable in _____ and Endotoxin - _____. Volume 2, page 3-393 includes the results for bioburden testing for production batches _____ and _____. It appears that a in-process bioburden and endotoxin specification should be established. Further, specifications should be established based on the manufacturing history, not a failure in GMP's. Please review the drug substance bioburden specification for their current manufacturing campaign to ensure that their specification is appropriate.

15. Volume 2, page 3-345 illustrates that _____ is used to clean the _____ System. Please review the cleaning validation, sanitization effectiveness, and bacteriostatic performance of the cleaning and storage solutions.

16. Volume 2, pages 3-397 and 4-406 describes the leachable _____ and carbohydrate (_____ from the _____ columns. Analysis of the _____ levels (column leachable) and _____ (_____ test) were performed for batch _____ and _____, and _____. Data showed that leached _____ is detected at concentrations between _____ to _____ at the

_____ and _____ pools. Please clarify whether this evaluation was performed for the first three _____ purifications, where levels would be the highest.

17. Please review validation for the following water systems: purified water, WFI produced by Reverse Osmosis and _____ and WFI produced by distillation. Additionally, review the most current six months of water monitoring for points of use servicing Building _____ filling line _____ located on the basement floor in Room _____ and Building _____ (_____ site), suites _____

18. Please review filter validation studies (extractable and bioburden) for the 0.22 micron _____ membrane used to sterilize the _____ sterile bulk drug product.

19. Throughout the drug substance manufacture, there are several filtration operations. Because there is an associated bioburden level following the filtration, microbial challenge in the product buffers is not necessary, however, the firm should have buffer-filter compatibility and extractable information available for review.

20. Please review sterilization validation for one of the following: bioreactor, largest and smallest portable and fixed holding tank used for the most downstream process, filling head.

21. Please review the cleaning validation of the following equipment: Bioreactor _____ largest and smallest mobile and fixed vessel, filling needles/heads, _____ lyophilizer. Additionally, obtain a complete list of multi-use equipment and change-over procedures.

22. Volume 4, page 3-704 describes the requalification of the _____ hot air tunnel used to depyrogenate _____ and _____ vials prior to entering _____ filling line. They performed an empty tunnel heat distribution study (_____ at _____ and _____ at _____) and a single full load study using both _____ and _____ vials. The acceptance criteria is _____ endotoxin reduction using _____ endotoxin spiked vials, _____ temperature distribution in an empty and loaded tunnel configuration, and _____ for _____ (V4, 3-675). The _____ vials failed the acceptance criterion of _____ in zone _____. Please review the investigation to include the preventative maintenance of this depyrogenation tunnel. In addition, the firm should have supporting studies demonstrating that the process is reproducible (i.e., more than one study using the same or larger vial sizes).

23. Volume 4, page 3-715 describes the requalification of the _____ stopper washer. The _____ washes and sterilizes the large (_____ and small (_____ stoppers for the _____ 20 mg/mL dosage forms.

Sterilization parameters included and evaluation of temperature and pressure correlation

thermocouples. During the prelicense inspection, please review the following: empty chamber heat distribution study and full chamber heat distribution study (mean temperature at mid-dwell). In addition, the firm should have supporting studies demonstrating that the process is reproducible (i.e., more than one study using similar stopper sizes).

24. Volume 4, page 3-676 describes the 1992 evaluation of the washing process for the — using endotoxin spiked stoppers. The washing cycle demonstrated a — endotoxin reduction for the — spiked stoppers. Simulect is a parenteral product, therefore, in addition to endotoxin reduction, the firm should have some data supporting particulate removal for stoppers.

25. Volume 4, pages 3-726 to 3-734 describes the sterilization requalification of stopper feeders number — and — for the — filling machine. The sterilization program parameters are — for —. The study evaluated biological indicator challenge on the cover and discharge tube, no temperature data using distribution thermocouples was submitted. During the prelicense inspection, please review temperature distribution data. Additionally, please verify the revalidation frequency.

26. Volume 4, pages 3-748 to 3-750 and 3-777 to 3-780 include a schematic and temperature charts for the SIP requalification of the filling machine — freeze dryer chamber and condenser. No narrative was included in the submission. Please review the validation study supporting these sterilization cycles.

27. At the time of submission, 6 months of stability data for the drug substance was submitted in support of this BLA. Storage of the bulk drug substance is in — screw cap — containers at —. Please review drug substance stability data (— and — for batches —.

28. At the time of submission, one lot of drug product (—) produced at pilot scale has been in the stability program for — 2 lots (— produced with drug substance using — and — in the culture medium and —) at — months; and one lot (—) at — months. Please review the drug product stability data for batches — and —. The testing protocol includes all specifications, except for endotoxin and sterility, which are tested initially and at the end.

II. Review Narrative

OVERVIEW

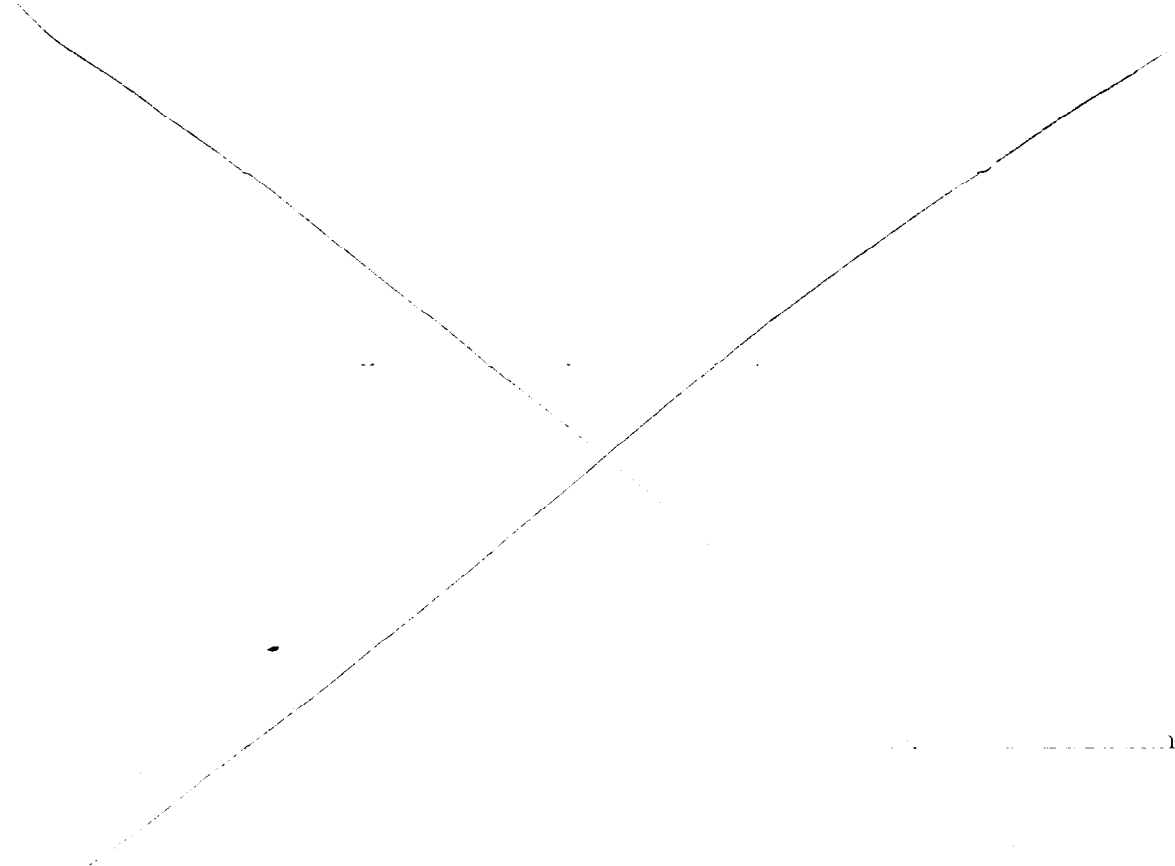
Novartis Pharmaceutical Corporation has submitted a BLA for the manufacture of the drug substance, basiliximab, and the drug product, Simulect Lyophilizate for Injection. This product is manufactured by Novartis Pharma AG, at their Basel, Switzerland location. The manufacture and control of basiliximab is performed by the _____ on the _____ campus of Novartis Pharma AG; production of the drug product, Simulect Lyophilizate for Injection, is done on the same site. Each vial contains 20 mg basiliximab, 7.21 mg monobasic potassium phosphate, 0.99 mg disodium hydrogen phosphate, 1.61 mg sodium chloride, 20 mg sucrose, 80 mg mannitol and 40 mg glycine, to be reconstituted in 5 mL of Sterile Water for Injection, U.S.P. The antibody functions as an immunosuppressant and is for use in renal transplantation to reduce the incidence of organ rejection.

METHOD OF MANUFACTURE

Cell Seed Lot System - Master Cell Bank - A vial from the Primary Seed Lot was used to prepare a Master Cell Bank (MCB). Cells were thawed and cultivated in serum-free medium, expanded in T-flasks, harvested, and resuspended in freezing medium containing fetal calf serum. Aliquots were filled into 100 vials, at _____ cells/vial, frozen, and stored in the vapor phase of a _____ storage tank. The MCB cells are at 20 passages after cloning, and viability before freezing was 95%. Representative vials of the MCB were shown to be free of adventitious contaminants and mycoplasma, and were thoroughly characterized.

Working Cell Bank - The working cell is prepared in Building _____ Room _____ (Cell Culture Laboratory). Vial _____ of the MCB was used to prepare a Working Cell Bank (WCB). The same MCB medium was used except that _____ was replaced by _____. Cells were grown in a T-flask and expanded into roller bottles. Cells were harvested, resuspended in freezing medium (without fetal calf serum), dispensed into vials and frozen, and stored in the vapor phase of _____ in Building _____. The WCB consists of _____ vials, containing _____ (passage _____ after cloning) with a viability of _____ before freezing. Representative vials of the WCB were shown to be free of adventitious contaminants and were characterized.

Cell Growth and Harvesting - Cultivation medium is prepared in _____ facility, Room _____ and sterile filtered into The innoculum for the seed bioreactor is prepared from one vial of the working cell bank into T-flasks. The transfer is performed in a laminar flow hood in Building _____ facility), Room _____. Cells are passed up to _____ times and expanded into roller bottles for up to _____ passages. Between _____ roller bottles (_____) are



End of Production Cells - Cells taken from production cultures (at commercial scale, for three process validation runs) in the late phase were used to establish an EPC. Cells were subcultured first in the production medium and then in the same medium used to prepare the WCB. Harvested cells were resuspended in freezing medium, dispensed into vials, frozen and stored in the vapor phase of _____. Representative vials of all three EPC were shown to be free of adventitious contaminants and mycoplasma. The EPC cells from the first run of the validation campaign were characterized.

Harvest - Harvest is collected in tank _____ at _____ and when the volume reaches _____ the supernatant is transferred to tank _____ which is also cooled to _____. Each transfer is considered a harvest lot. The first harvest lot from the first _____ days (cultivation days _____) is discarded due to low antibody concentration. Typically, a harvest lot contains _____ of _____ to _____ harvest lots are produced for purification (_____. The commercial purification process has an overall efficiency of approximately _____ and typically yields _____ of bulk drug substance per batch.

Purification and Downstream Processing - For full scale production the sequence of operations has been revised (from pilot production runs; see section 1.7) to give a logical separation of the steps designed for virus inactivation and removal, and the later steps for purification of the drug substance. The procedures and purpose of the individual purification process steps are shown in Table 2 below.

In step 1, _____ of the harvest lot is diluted with _____ WFI from tank _____ to lower the salt concentration. The diluted harvest is loaded onto the _____ exchange column in Building _____ facility, Room _____. The antibody binds to the column and eluted with _____ (_____. The product volume is approximately _____.

In step 2, the pH is adjusted to _____ with _____ and stirred for _____. This step inactivates potential retrovirus contaminants. Following incubation, the solution is adjusted to pH _____ with _____ filtered through _____ tandem prefilters followed by a _____ micron filter. The product volume is approximately _____. This operation is performed in Building _____ facility, Room _____.

In step 3, the pH adjusted solution is filtered through a _____ filter followed by a _____ micron filtration. The product is stored in a portable tank and stored at _____ in Building _____ facility, Room _____. Several batches or lots are pooled and loaded onto the column (typically _____ batches are produced and _____ of the _____ discarded).

In step 4, the filtered solution is loaded onto a equilibrated _____ column and the column is washed with 12 column-volumes of _____. The antibody is eluted with _____. The eluted product solution is adjusted to _____ and _____ micron filtered. The column is subsequently sanitized with _____. This operation is performed in Building _____ facility _____, Room _____.

In step 5, the pH adjusted product solution is pumped onto a equilibrated (_____ column. The flowthrough is diluted with _____ volumes of water, _____ micron filter, and stored at _____. The product volume is approximately _____. The column is subsequently regenerated with _____) and sanitized with _____.

This operation is performed in Building _____ facility _____, Room _____.

In step 6, the diluted product solution is loaded onto a equilibrated (_____ column, washed with _____, and eluted with _____. The product peak is collected, _____ micron filtered, and stored at _____. The product volume is approximately _____. The column is subsequently sanitized with _____. This operation is performed in Building _____ facility _____, Room _____.

In step 7, the antibody is concentrated to _____ diafiltered in _____ micron filtered, and stored at _____. The product volume is approximately _____. The _____ system is cleaned with _____.

_____ This operation is performed in Building _____, facility
 _____ Room _____

In step 8, the bulk is dispensed in _____ aliquots into _____
 deprogenated, sterile _____ bottles. The bulk is
 transferred to Building _____ and stored below _____.

Table 2

| Step | Procedure | Purpose | In-Process Controls | Typical Yield |
|------|-----------|---------|---------------------|---------------|
| 1 | | | | |
| 2 | | | | |
| 3 | | | | |
| 4 | | | | |
| 5 | | | | |
| 6 | | | | |
| 7 | | | | |
| 8 | | | | |

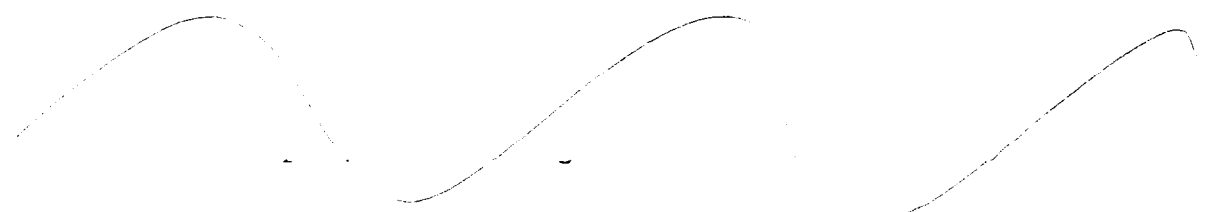
Volume 2, page 3-129 describes the air quality classification of various rooms in the _____ facilities. The area classifications are listed as critical, controlled, or unclassified. The monitoring frequency is monthly for controlled areas and twice a month for critical areas. The firm should be advised that CBER recommends in critical areas viable and nonviable monitoring should be performed daily during dynamic conditions.

Validation for cell growth, harvesting, and antibody purification - The scale of cell cultivation (_____ bioreactor) is the same as used at pilot scale. _____ validation batches

were produced at production scale to compare the performance of the cell growth procedures and the quality of the antibody with pilot material. Batches _____ and _____ are extensively documented; see section 2.4.2 (of Section 3 of the BLA) for details, and also Tables 3 and 4 of section 2.6.2 (of Section 3 of the BLA). At the cell cultivation stage, variability in the in-process parameters has been observed, requiring fine tuning of the process. During the continuous cultivation there can be some fluctuation of cell density and antibody titer; the specific productivity of the cells, however, remains rather constant. The fluctuations in cell density can be (partially) compensated by adjusting the dilution rate to maintain the nutritional environment in the bioreactor. The quality of antibody product harvested at different time points during continuous cultivation remains high despite any variability in process parameters. Cell cultivation is carried out under sterile conditions, whereas downstream processing is done at low bioburden conditions. Determination of total microbial counts on the bulk harvest and at various steps during purification shows that the bioburden is typically below _____. This low bioburden is also reflected in the very low levels of endotoxin, below the detection limits (_____ of the assay). The removal of process-related contaminants has been investigated for the _____ cited production batches. Step 4 in the antibody purification uses a _____ column, and the column material itself can leach and subsequently contaminate the product. _____ was determined using an _____ test. Samples of the eluate from Step 4 showed a low level (_____ of _____) of _____ leaching. Samples tested after Steps 5 and 6 of the purification showed that after the _____ purification (Step 6) the amount of _____ detectable had been reduced to below _____, i.e., less than the quantifiable limit. The results for removal of _____ are consistent with data from pilot scale studies. Removal of _____ was similarly investigated, using a sensitive _____ test. Samples after Step 3 (_____ filtration) showed the presence of substantial amounts of _____ (values above _____). Purification on the _____ column removed most of the contaminating _____ (circa a _____ reduction) and the _____ chromatographies resulted in a further reduction; the final values were below _____ and are better than found at pilot scale. _____ was determined by _____ at several steps in the purification process. The _____ column (Step 4) and the _____ column (Step 5) were the main steps for _____ following the latter step, and reflected in the final product, the values for _____ were _____ the detection limit for the assay. This corresponds to _____ of _____ per 20 mg vial of drug product. The levels of the culture medium ingredients _____ and _____ were shown to be reduced to low levels (i.e., levels of _____ basiliximab) by factors of _____ and _____ respectively after the _____ chromatography step; the level

of _____ is probably further reduced after the _____ step since it would be expected to be washed out of the (ion-exchange) column. Low levels of multimeric variants of the antibody are found during all steps of the purification. These variants, which are mainly dimers, amount to less than _____ of the drug substance and are shown to be further reduced at Step 6 so that levels in the final product are almost negligible. The purification process did not appreciably alter the isoform distribution of basiliximab, and as shown by batch analyses.

Viral Clearance - The clearance of viruses during the purification process was therefore validated in an exact scale-down of the production process. The studies were conducted at _____ and the validation was carried out according to both the FDA Points to Consider document and the CPMP Guidance on Viral Validation Studies. It is known that murine hybridoma cell lines secrete an endogenous virus and that this is also the case for the cell line developed for the production of basiliximab. This was taken into account in selecting the model viruses for the validation of clearance. _____ types were selected: _____



A validation study at the pilot scale purification process had shown that _____ and _____ are not cleared at the pH inactivation step, and that no clearance of _____ can be expected at the _____ step. Thus these particular tests were not repeated in the production-scale validation. The _____ step was not tested as it had not been found effective in pilot scale validation. For the endogenous _____ virus there is a high and reproducible clearance of virus with all _____ steps tested contributing to the overall result. The number of virus-like particles determined in the bulk harvest is typically _____. Assuming a worst-case scenario with _____ virus particles per liter of bulk harvest culture and a volume of _____ culture broth required to produce one dose of the drug product (2 x 20 mg), then the _____ reduction confers a safety margin of _____ compared with the recommended (ICH Guidelines) safety margin of 6 logs. The other three model viruses are also removed effectively, with each process step contributing to viral clearance. The validation results indicate that an endogenous murine virus and a representative selection of potential adventitious viruses are effectively cleared.

Drug Substance Stability and Container/Closure System - Bulk basiliximab new drug substance made at commercial scale is stored at below _____ in _____ containers with screw caps. During early development bulk new drug substance was stored in glass bottles at _____, while a stability study was conducted on the three pilot batches (_____ at several temperatures (_____. No significant decrease in biological activity could be demonstrated at any of the temperatures examined. Evidence of degradation was observed at _____ at _____ and at the _____ and _____ indicated that basiliximab was stable at _____ and _____ but _____ indicated that accumulation of aggregates was greater at _____ than at _____. Based on this preliminary data, the storage temperature for bulk new drug substance was therefore changed to below _____.

Drug Product, Method of Manufacture - Volume 4, page 3-671 includes an European Union (EU) air cleanliness table. The table indicates that a Class D area has a 0.5 micron nonviable specification of 100,000. The European Community (EC) Guide does not define an operational specification for a Class D area. Included in the table below is a comparison of the European Community and the United States standards.

| Operational (Dynamic) | | At Rest (Static) | |
|-----------------------|----------------|------------------|---------------|
| E.C. Guide | U.S. Guide | E.C. Guide | U.S. Guide |
| Grade A | Class 100 | Grade A | Class 100 |
| Grade B | Class 10,000 | Grade B | Class 100 |
| Grade C | Class 100,000 | Grade C | Class 10,000 |
| Grade D | Not Applicable | Grade D | Class 100,000 |

In addition, the submission did not describe viable limits, pressure differentials, or air flow rates in any critical and controlled areas.

Manufacture of Simulect, Lyophilizate for Injection is manufactured by weighing approximately _____ of Water for Injection in a glass vessel; the excipients are added by weight, in the following order _____.

_____ . The drug substance solution is added to the excipient solution, followed by sufficient WFI for the batch size. The solution is 0.2 micron pre-filtered, and then sterile filtered (0.2 micron filter) and filled into vials in the Aseptic Filling Unit. The vials are lyophilized in the aseptic compact freeze drier unit, closed, and then sealed. The vials are 100% visually inspected for particulate matter.

Component preparation (stopper washing) is performed on the _____ floor in Rooms _____ and _____ in Building _____. Compounding is performed under a laminar flow in Room _____, a Class _____ area. Stoppers are washed and sterilized in a _____ machine located in a Class _____ area (Room _____. Following compounding, the bulk product solution is 0.2 micron (_____) filtered into a sterile portable tank. The time from compounding to the first filtration is _____. In-process bioburden testing is performed for each batch by sampling bulk solution on the upstream side of the first _____ filter. The specifications are _____

_____ A second _____ micron filtration is performed during filling operations. In-process bioburden testing is performed for each batch by sampling bulk solution on the upstream side of the final filter. The specifications are _____ is _____ The formulation for the 20 mg/vial strengths

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correspond to the theoretical filling volume of _____ manufacture actually uses a _____ overfill to permit withdrawal of the nominal dose from the single-dose container. The nominal 20 mg/vial strength thus actually contains 21.5 mg of basiliximab.

The final product vial contains 20 mg of basiliximab drug substance (a _____ overfill is used in manufacture to allow withdrawal of the correct dosage, so the final vial actually contains 21.5 mg of basiliximab). Lyophilizate contain standard excipients (buffering salts, glycine, sucrose, and mannitol) and the active substance. When reconstituted in the vehicle provided, the solution is isotonic, at physiological pH _____), sterile, and pyrogen free. For clinical trials, Simulect was available in vials of _____ 20-mg strengths. Immediately prior to administration, Lyophilizate are reconstituted by injecting vehicle into the vial (5 mL for the 20-mg strength or _____) and the Lyophilizate redissolved with gentle swirling or inversion. Reconstituted medication can be administered either as a bolus intravenous injection or diluted to a volume of 50 mL or greater with normal saline or dextrose 5% and infused intravenously over 20-30 min.

Drug formulations Drug Product Tests and Specifications

| Physical properties | Requirements |
|---------------------|--------------|
| | |
| | |
| | |
| | |
| | |
| Identity | |
| | |
| | |
| | |
| Purity | |
| | |
| | |
| | |
| Assay | |
| | |
| | |
| | |
| Other | |
| | |
| | |
| | |

| Other | |
|-------------------------------|--------------------------------------|
| Abnormal toxicity type B | The sample meets the requirements of |
| (safety test for biologicals) | Ph.Eur. and 21 CFR 610.11 |

Drug Product Stability and Container/Closure System - The container/closure system for the 20 mg/vial strength of Simulect Lyophilizate is a 6 mL glass vial (_____), with a _____ coated with a _____ . The seal is a _____ a _____

The vials are made of _____ glass _____ coated with a _____ from _____ . The stoppers are made of _____ (_____) coated with a _____ from _____ . The seal (nonproduct contact) consists of a _____ cover and a _____ from _____

The proposed storage temperature for the drug product is 2-8°C (U.S.P. Refrigerated storage conditions) and an expiration dating of _____ is proposed. The usual extension of expiration date based on actual data is planned. The commercial formulation of the drug product is the same as that used for the Phase III batches produced at pilot scale. Stability results for a pilot batch (_____) of the lyophilized product stored for _____ at _____ storage) are within specification. Data for _____

_____ Drug product batches on stability are given below. The testing protocol includes all specifications, except for _____ and _____

Drug Product Batches on Stability at _____ in the market container/closure

| Drug Product Batch No. | Drug Substance Batch No. | Longest Point (at submission) |
|------------------------|--------------------------|-------------------------------|
| _____ | _____ | _____ |
| _____ | _____ | _____ |
| _____ | _____ | _____ |
| _____ | _____ | _____ |

Batch _____ and the drug substance batch _____ were produced at pilot scale. Drug substance batch _____ was produced using _____ in the inoculum, and this batch and the drug product batch _____ is limited to technical use only (e.g., stability). Drug substance batches _____ and _____ were from the drug substance process validation studies. Similarly, drug product batches _____ and _____ are from drug product validation studies.

Container/Closure integrity was demonstrated using a microbial challenge. _____ units were filled with _____ and challenged in a suspension of _____ with negative and positive pressure. The units are incubate at _____ for _____

Volume 4, pages 3-755 to 3- describes filling equipment loads for Autoclave _____. An empty chamber heat distribution study demonstrated that mid-dwell temperatures were _____ between the hottest and warmest spots. The acceptance criteria is \pm _____ and an _____. A full load using filling equipment was performed using a cycle of _____ for _____ using _____ distribution thermocouples along with biological indicator challenge. Thermocouples placed in the filling equipment logged minimum and maximum temperatures of _____ and _____. Regualification is performed annually. I found their studies satisfactory.

Investigational Product/Formulation Comparability - The proposed market formulation containing mannitol as an excipient has been used in batches made during and after 1994, so that the formulation proposed for marketing has had extensive clinical usage. Earlier batches (1991) did not contain _____, but were otherwise nearly identical to the market formulation. The drug product is made at the same campus (although the actual buildings involved have changed) and the method of manufacture, aseptic fill followed by lyophilization, is the same for investigational and commercial product. The batch sizes (vials) for pilot and commercial production are similar. The specifications and tests for investigational and commercial products are also the same, but the procedure for determination of biological activity (a _____ assay) has been automated. There is thus no significant difference between investigational and market products. However, the manufacture of basiliximab drug substance batches on the commercial scale differs from the manufacture of basiliximab for the clinical/investigational batches. Extensive analytical comparison of commercial scale drug substance batches with the reference standard (lot _____ made on pilot scale) demonstrate that commercial batches are fully comparable and equivalent to

pilot scale material. The viral clearance capability of the revised commercial process has been re-validated and found to be satisfactory. The changes in going from pilot scale to commercial drug substance manufacture can be summarized as follows: Both scales of operations used a _____ bioreactor; for pilot operations the harvest size was _____ rather than the _____ commercial size, and the operations were in different buildings on the same site. The medium for cell growth on commercial scale has been revised to include _____ (at _____ concentration), since these have been found to yield optimal growth during cultivation. The media are otherwise identical. The purification equipment capacity for commercial manufacture has been increased _____ over that of pilot scale through use of equipment with increased column diameter. The column packings are unchanged. Because of the scale-up, operations are done at _____ for the first _____ steps. On the pilot scale all operations were done _____ The sequence of purification has been revised. The _____. The commercial process purifies each harvest lot from _____ independently through Step 3 (_____. All Step 3 lots from one cell through the rest of the purification scheme; i.e., _____. Bulk new drug substance is now stored frozen at below _____ rather than at _____

Environmental Assessment

Novartis has requested categorical exclusion for preparing an Environmental Assessment.

Page 20 - Ref. No. 97-1251